BlueCross BlueShield Federal Employee Program.

# FEP Medical Policy Manual

## FEP 2.04.75 Genetic Testing of CADASIL Syndrome

**Effective Policy Date: July 1, 2023**

**Original Policy Date: March 2012**

**Related Policies:**

None

# Genetic Testing of CADASIL Syndrome

## Description

### *Description*

*Variants in the NOTCH3 gene have been causally associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Genetic testing is available to determine if pathogenic variants exist in the NOTCH3 gene for patients with suspected CADASIL and their family members.*

## OBJECTIVE

The objective of this evidence review is to determine whether genetic testing improves the net health outcome in individuals with suspected CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) syndrome and in asymptomatic individuals with family members who have CADASIL syndrome.

## POLICY STATEMENT

Genetic testing for a NOTCH3 variant to confirm the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome in an individual may be considered **medically necessary** under the following conditions:

- Clinical signs, symptoms, and imaging results are consistent with CADASIL, indicating that the pretest probability of CADASIL is at least in the moderate-to-high range (see the Policy Guidelines section); and
- The diagnosis of CADASIL is inconclusive following alternative methods of testing, including magnetic resonance imaging.

# POLICY GUIDELINES

Genetic testing for NOTCH3 comprises targeted sequencing of specific exons (eg, exon 4 only, exons 2-6), general sequencing of NOTCH3 exons (eg, exons 2-24 or all 33 exons), or targeted testing for known NOTCH3 pathogenic variants. Skin biopsy should be reserved for patients where NOTCH3 genetic testing is inconclusive (e.g. variants of uncertain significance).

The probability that cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is present in an individualized assessment depends on numerous factors such as family history, symptoms, imaging results, and other specialized testing such as skin biopsy.

Pescini et al (2012) attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present. Table PG1 summarizes the pooled frequency of clinical and radiologic features, and the points assigned for each finding. The authors recommended that a total score of 14 be used to select patients for testing, because this score resulted in a high sensitivity (96.7%) and a moderately high specificity (74.2%).

### Table PG1. Pooled Frequency of Clinical and Radiologic Features

| Features | No. With *NOTCH3* Variant | Percent With *NOTCH3* Variant | Points |
|---|---|---|---|
| *Clinical* | | | |
| Migraine | 239/463 | 52% | 1 |
| Migraine with aura | 65/85 | 76% | 3 |
| Transient ischemic attack/stroke | 380/526 | 72% | 1 (2 if <50 y) |
| Psychiatric disturbance | 106/380 | 28% | 1 |
| Cognitive decline | 188/434 | 43% | 3 |
| *Radiologic* | | | |
| LE | 277Pescini /277 | 100% | 3 |
| LE extended to temporal pole | 174/235 | 74% | 1 |
| LE extended to external capsule | 228/303 | 75% | 5 |
| Subcortical infarcts | 210/254 | 83% | 2 |

Adapted from Pescini et al (2012)
LE: leukoencephalopathy; No: number.

## Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was implemented for genetic testing medical evidence review updates in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organisation, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

**Table PG2. Nomenclature to Report on Variants Found in DNA**

| Previous | Updated | Definition |
|---|---|---|
| Mutation | Disease-associated variant | Disease-associated change in the DNA sequence |
| | Variant | Change in the DNA sequence |
| | Familial variant | Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives |

**Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification**

| Variant Classification | Definition |
|---|---|
| Pathogenic | Disease-causing change in the DNA sequence |
| Likely pathogenic | Likely disease-causing change in the DNA sequence |
| Variant of uncertain significance | Change in DNA sequence with uncertain effects on disease |
| Likely benign | Likely benign change in the DNA sequence |
| Benign | Benign change in the DNA sequence |

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

## Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

# BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient"s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

# FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing of *NOTCH3* is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

# RATIONALE

## Summary of Evidence

For individuals with suspected *cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (*CADASIL) syndrome who receive *NOTCH3* genetic testing, the evidence includes case reports, case series, and genotype-phenotype correlation studies evaluating the clinical validity and genetic testing yield for *NOTCH3*. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. The clinical validity studies have demonstrated that a *NOTCH3* pathogenic variant is found in a high percentage of patients with a clinical diagnosis of CADASIL, with studies reporting a clinical sensitivity of 90% to 100%. Limited data on specificity derives from testing small numbers of healthy controls, and no false-positive *NOTCH3* pathogenic variants have been reported in these populations. The diagnostic yield studies have reported a variable yield, ranging from 10% to 54%. These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders. No direct evidence was identified demonstrating outcome improvements associated with genetic testing for CADASIL. However, a chain of evidence can be constructed to demonstrate that identification of a *NOTCH3* pathogenic variant establishes the diagnosis of CADASIL without the need for a skin biopsy and reduces the need for other diagnostic tests used to exclude other conditions in a differential diagnosis. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with family members who have CADASIL syndrome who receive targeted genetic testing for a known *NOTCH3* familial variant, the evidence is limited. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. For asymptomatic family members of an individual with known CADASIL, knowledge of the presence of a familial variant may lead to changes in lifestyle decisions for the affected individual (eg, reproduction, employment). However, the impact of these lifestyle decisions on health outcomes is uncertain, and there are no interventions for asymptomatic individuals that are known to delay or prevent disease onset. A chain of evidence can be constructed to demonstrate that identification of a *NOTCH3* familial variant predicts future development of CADASIL in an asymptomatic individual, eliminates the need for additional diagnostic testing, allows for earlier monitoring for development of systems, aids in reproductive planning, and helps determine the likelihood of an affected offspring. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with family members who have CADASIL syndrome whose genetic status is unknown who receive *NOTCH3* genetic testing, the evidence is limited. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. For asymptomatic family members of an individual with known CADASIL whose genetic status is unknown, knowledge of the presence of a *NOTCH3* pathogenic variant may lead to changes in lifestyle decisions for the affected individual (eg, reproduction, employment). However, the impact of these lifestyle decisions on health outcomes is uncertain, and there are no interventions for asymptomatic individuals that are known to delay or prevent disease onset. A chain of evidence can be constructed to demonstrate that identification of a *NOTCH3* pathogenic variant predicts future development of CADASIL in an asymptomatic individual, eliminates the need for additional diagnostic testing, allows for earlier monitoring for development of systems, aids in reproductive planning, and helps determine the likelihood of an affected offspring. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

# SUPPLEMENTAL INFORMATION

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

No guidelines or position statements with US representation or that were informed by a systematic review were identified.

## U.S. Preventive Services Task Force Recommendations

Not applicable.

## Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

# REFERENCES


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## POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

| Date | Action | Description |
|---|---|---|
| March 2012 | New policy | |
| December 2012 | Replace policy | Updated with literature review and updated references. Policy statement unchanged. |
| December 2013 | Replace policy | Policy updated with literature review. Reference 13 added. Medically necessary statement added for patients with high likelihood of disorder, in whom diagnosis cannot be made by other methods. Title revised to include all genetic testing for CADASIL syndrome and "syndrome, added to title and policy statements. |
| December 2014 | Replace policy | Policy updated with literature review through September 6, 2014.References 14, 16, and 24 added. Policy statement unchanged. |
| June 2017 | Replace policy | Policy updated with literature review through February 23, 2017;reference 20 added. The policy is revised with updated genetics nomenclature. "Mutations "changed to "variants, in policy statements. Requirement for skin biopsy removed from medically necessary policy statement for testing of symptomatic patients; medically necessary statements added for testing in asymptomatic and presymptomatic family members of individuals with CADASIL. |
| June 2018 | Replace policy | Policy updated with literature review through February 5, 2018; no references added. Statements removed for testing in asymptomatic and presymptomatic family members of individuals with CADASIL due to benefit application of testing to diagnose and/or manage a patient's existing medical condition. |
| June 2019 | Replace policy | Policy updated with literature review through February 5, 2019; no references added. Policy statements unchanged. |
| June 2020 | Replace policy | Policy updated with literature review through April 2, 2020; European Academy of Neurology consensus recommendations added. Policy statement changed to remove skin biopsy requirement prior to genetic testing. |
| June 2021 | Replace policy | Policy updated with literature review through February 25, 2021; no references added. Policy statements unchanged. |
| June 2022 | Replace policy | Policy updated with literature review through January 17, 2022; no references added. Policy statements unchanged. |
| June 2023 | Replace policy | Policy updated with literature review through January 16, 2023; no references added. Minor editorial refinement to policy statement; intent unchanged. |